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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/735,408	12/12/2003	Richard Storer	06171.105064 IDX 1024	2099
20786 7590 01/09/2008 KING & SPALDING LLP 1180 PEACHTREE STREET ATLANTA, GA 30309-3521			EXAMINER KRISHNAN, GANAPATHY	
			ART UNIT 1623	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/735,408	Applicant(s) STORER ET AL.	
	Examiner Ganapathy Krishnan	Art Unit 1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 30 October 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 20,23-28,31-44,50,64-68 and 89-107 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 20, 23-28, 31-44, 50, 64-68 and 89-107 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>11/07</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

A Request for Continued Examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed 10/30/2007 has been entered.

The Request for Continued Examination filed 10/30/2007 has been carefully considered. The following information provided in the amendment affects the instant application:

1. Claims 1-19, 21-22, 29-30, 45-49, 51-63 and 69-88 have been canceled.
2. New Claims 93-107 have been added.
3. Remarks drawn to rejections under 35 USC 103 and obviousness-type double patenting of record in the previous office action.

Claims 20, 23-28, 31-44, 50, 64-68 and 89-107 are pending in the case.

Information Disclosure Statement

Foreign language references listed in the Information Disclosure Statement, for which no English translation has been provided, have not been considered. If an English abstract has been provided for a foreign language document then only the English abstract has been considered.

Claim Objections

Claims 35 and 102 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to

cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim 35, which depends from claim 33, recites that the total time for synthesis is about 60 hours. This is 2.5 days and falls outside the range, about 5 days to about 14 days, recited in parent claim 33 and is not further limiting.

In claim 102, line 1, the period after the terms 'step a' should be deleted.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 36 and 92 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 36 is drawn to the process of claim 20 and recites adding CaO to an aqueous solution of D-fructose in step (a). This same step is recited as the first step in the process of claim 20. Do applicants intend adding more CaO to the aqueous solution of D-fructose in step (a) of claim 36? It is not clear what applicants intend. This recitation is also seen in claim 92.

Double Patenting

The rejection of Claims 20-28, 36, 50 and 64-67 provisionally on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-2 of

copending Application No. 10/882,893 ('893 application), made of record in the previous office action has been rendered moot by cancellation of claims 1-2 in the '893 application.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 20, 21-28, 31-44, 50, 64-68, 89-92 are rejected under 35 U.S.C. 103(a) as being unpatentable over BeMiller et al (Methods in Carbohydrate Chemistry, 1963, 2, 484-485, IDS document # HK) in combination with The Merck Index (12th edition, 1996, pages 274-275), Ault (Techniques and Experiments for Organic Chemistry, 5th Edn., 1987, 105-113), Sundberg et al (Advanced Organic Chemistry, Part B, 1990, pages 232 and 235-236), McFarlin (J. Am. Chem. Soc. 1958, 80, 5372-76) and Piccirilli et al (J. Org. Chem. 1999, 64, 747-54; IDS document # HH).

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

BeMiller et al teach the conversion of D-fructose (I) to 2-C-methyl-D-ribonolactone (II). The transformation is carried out using calcium hydroxide (aqueous), carbon dioxide and oxalic acid (pages 284-285, Procedure). The calcium hydroxide is added to a solution of D-fructose in boiled water. This mixture is then saturated with carbon dioxide and oxalic acid is added, warmed and filtered. The filtrate is then treated with Amberlite, acid form, and then the washing is concentrated to get the ribonolactone. BeMiller, thus teaches step (a) in instant claim 20, steps (a)-(b) in claim 36 and steps (a)-(d) in claim 92. However, BeMiller et al do not teach specifically the use of aqueous CaO, the reduction of the carbonyl group of the ribonolactone or the formation of the benzoyl derivative of the furanose.

The Merck Index teaches that calcium oxide is soluble in water forming calcium hydroxide (page 275, entry # 1733) but calcium hydroxide is only slightly soluble in water (page 274, entry # 1716). This is the reason why BeMiller adds calcium hydroxide to the hot solution. Reacting aqueous CaO with fructose as instantly claimed is same as the reaction taught by BeMiller et al. The use of calcium oxide is also preferable in view of Merck Index since it is more soluble in water and dissolves to produce the calcium hydroxide needed for the said

conversion. No heating is necessary. The dissolution of calcium oxide in water is also exothermic and the heat generated will help dissolve any undissolved starting materials.

Ault, drawn to techniques in organic chemistry, teaches that extraction is a general method used to separate organic substances (page 105, section 13 and page 110-112). In the process of Bemiller, it can be seen that calcium ions, and excess acid will remain as impurities and need to be separated from the desired product. Separation of the desired product from these impurities can be achieved by extraction as taught by Ault. One of ordinary skill in the art also knows that this is a routine procedure used in any organic synthetic process for separating the desired product from impurities and would include the extraction step in the process of Bemiller.

Sundberg et al teach the reduction of a lactone carbonyl to the corresponding alcohol using alkoxyaluminumhydride reagent (page 236). This reagent is also known as Red-Al (page 235, lines 8-9). Even though the reducing agent is not lithiumtri(t-butoxy)aluminum hydride as instantly claimed, one of ordinary skill in the art will recognize that it is very similar and performs the same function. Sundberg et al also teach (page 232, Table 5.2) that lithiumtri(t-butoxy)aluminum hydride also reduces a carbonyl group to an alcohol.

According to McFarlin et al lithiumtri(t-butoxy)aluminum hydride is very stable and a mild reducing agent and is soluble in several solvents (page 5372 abstract; page 5373, Table I).

Piccirilli et al teach the use of benzoyl derivative of ribofuranose (page 748, structure 1) in synthesis of 2'-branched nucleosides. He also discloses that 2'-alkyl substituted ribofuranoses are useful for the syntheses of 2'-C-branched nucleosides since such nucleosides show cytotoxicity towards leukemic cell lines and might be useful in gene regulation (see introduction). This means that a synthesis of protected 2'-C-branched ribofuranoses from readily

available starting materials like D-fructose would be very useful. One of skill in the art would also extend the instant process to protected ribofuranoses since Piccirilli teaches the use of such protected sugars for the synthesis of nucleosides. Hence one of skill in the art would want to extend the instant process to include protected sugars.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the prior art and use it in the processes as instantly claimed since the process steps and reagents for the carrying out the same are seen to be taught in the prior art.

One of ordinary skill in the art would be motivated to use the process of the prior art since the process for the preparation of the lactone and the corresponding alcohol as taught by the prior art involve simple manipulations and the use of mild reagents as taught by McFarlane. One of skill in the art would want to use process steps that are art tested and known to work well to yield the desired product. It is well within the purview of one of ordinary skill in the art to extend the scope of the process to other solvents and reagents (reducing agents and protecting groups) for the purpose of optimizing the yield of the desired product and the process steps. It is also well known in the art to speed up reactions by using higher temperatures.

Claims 93-100 are rejected under 35 U.S.C. 103(a) as being unpatentable over BeMiller et al (Methods in Carbohydrate Chemistry, 1963, 2, 484-485, IDS document # HK) in combination with The Merck Index (12th edition, 1996, pages 274-275), Ault (Techniques and Experiments for Organic Chemistry, 5th Edn., 1987, 105-113), Sundberg et al (Advanced

Organic Chemistry, Part B, 1990, pages 232 and 235-236), McFarlin (J. Am. Chem. Soc. 1958, 80, 5372-76) and Piccirilli et al (J. Org. Chem. 1999, 64, 747-54; IDS document # HH).

The teachings of BeMiller, Merck Index, Ault, Sundberg, McFarlin and Piccirilli are elaborated above.

Piccirilli, further teaches the reaction of a protected ribose with a protected activated cytosine (persilylated 4-N-benzoylcytosine in the presence of SnCl_4 (Lewis acid) to make the 2'-C-methylcytidine product, which is also deprotected with sodium hydroxide (Scheme 1, page 748, conversion of structure 1 to structures 2a and 2b). The benzoyl protected cytosine is activated by reacting it with hexamethyldisilazane (HMDS; page 752, left column, third full paragraph in Experimental section). This teaching of Piccirilli covers the limitations of instant claims 93-95 and 97-99. However, Piccirilli does not teach the use of other silylating agents, Lewis acids and the use of sodium ethoxide as the base for deprotection of the 2'-C-methyl cytidine.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the prior art and use it in the processes as instantly claimed since the process steps and reagents for the carrying out the same are seen to be taught in the prior art.

One of ordinary skill in the art would be motivated to further include the step of reacting the protected 2-C-methyl-ribofuranose with a protected activated cytosine to make the corresponding nucleoside, as instantly claimed since the method of Piccirilli gives 2-C-methylnucleosides in very high yields. Such nucleosides are important from a synthetic point of view since they show antileukemic properties and are also useful in gene regulation (see

Piccirilli, introduction). The method of the prior art also uses the readily available D-fructose for making the glycoside moiety. One of skill in the art would want to use process steps that are art tested and known to work well to yield the desired product. It is well within the purview of one of ordinary skill in the art to extend the scope of the process to other solvents and reagents (reducing agents, protecting groups, Lewis acids, silylating agents, etc.) for the purpose of optimizing the yield of the desired product and the process steps.

Claims 101-107 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tam et al (US 4,837,311) in view of Chen et al (Heterocycles, 1989, 28(2), 593-601), Zemlicka (Nucleic Acid Chem., 1991, 4, 183-188) and Sundberg et al (Advanced Organic Chemistry, Part B, Third Edition, page 147).

Tam et al, drawn to nucleosides, teaches that selective protection of the 5' hydroxyl or the amino group of a nucleoside with conventional blocking group is known in the art. The general methods for the same are well known to one of skill in the art (col. 17, lines 10-36). This means that these two steps as instantly claimed can be performed by one of skill in the art on the branched cytosine of the instant process using any of the conventional protecting groups.

Chen et al teach the selective acylation of ribonucleosides with acylimidazole in the presence of bases to yield selectively the 3'-esterfied nucleoside (page 594, lines 7-19). The ratio of 2'O-acyl derivative to the 3'-O-acyl derivative is 3:7. Chen also teaches the esterification of nucleosides with different bases. This teaching of Chen shows that selective esterification of the 3' hydroxyl group on the ribose moiety can be achieved. However, Chen et al do not teach the esterification of a C-2'-branced nucleoside or esterification using a protected amino acid and

carbodiimide as the coupling agent. One of skill in the art will also recognize from Chen's teaching that the same selective acylation can be done on the ribose moiety of other ribonucleosides as well using activated carboxyl groups, similar to that used by Chen.

Zemlicka teaches the esterification of the 3' hydroxyl of adenosine using N-benzyloxycarbonyl protected L-phenylalanine (a protected amino acid) in the presence of dicyclohexylcarbodiimide (DCC, coupling agent) and triethylamine (base) in dimethylformamide (DMF) as the solvent (page 185, last paragraph through page 197 end). However, the ribofuranosyl nucleoside used in the process of Zemlicka is not a 2'-branched nucleoside. Here again one of skill in the art will recognize that the 3'-esterification of a branched nucleoside as instantly claimed can be carried out using a carbodiimide as the coupling agent.

Sundberg et al, drawn to general methods of esterification, teach that carbodiimides is an activating agent used to convert carboxyl group to reactive acylating agents. Carbodiimides like DCC have been widely applied in the coupling of amino acids. The combination of carboxyl activation by carbodiimide and catalysis by dimethylaminopyridine (DMAP) is a very useful reaction for activation of carboxylic acids for reaction with hydroxyl group for making esters (page 147, lines 11-21).

One of skill in the art would prefer to use carbodiimide as the coupling agent in the esterification step taught by Chen since Sundberg teaches that it has been used with amino acids for coupling. The activation of the carboxyl group by carbodiimide is also very similar to that by imidazole as taught by Chen. One of skill in the art would expect it to work as well as the imidazole method of Chen.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to include the process steps and reagents as instantly claimed since such process steps and reagents have been shown in the prior art to be used for performing the protection, deprotection and esterification steps on closely analogous ribonucleosides.

One of skill in the art would be motivated to use the process steps as instantly claimed since they have been art tested and shown to work well and yields of the desired products are also high.

Response to Applicants Arguments

Applicants' have traversed the rejection under 35 USC 103(a) of record in the previous action arguing that:

1. The Examiner has provided no reason why one of skill in the art would modify the process of Bemiller to use the specific step of adding CaO to a solution of fructose. Bemiller's process works for the intended purpose without the use of CaO.

2. Sundberg teaches that lithium methoxyethoxyaluminum hydride may be used to reduce lactones to lactols but is silent regarding the use of lithium tri-t-butoxy aluminum hydride and that reduction of esters is slower using lithium tri-t-butoxy aluminum hydride. One of skill in the art would not be motivated to use the weaker lithium tri-t-butoxy aluminum hydride reagent for reduction.

3. The example provided by McFarlin for the reduction of an ester using lithium tri-t-butoxy aluminum hydride failed.

Applicants' arguments are not found to be persuasive.

The motivation for using CaO instead of calcium hydroxide in the process of BeMiller is explained in the 103(a) rejection above in view of The Merck Index.

Sundberg teaches the reduction of lactone to lactol using the closely related lithium methoxyethoxyaluminum hydride. He need not specifically teach the use of lithium tri-t-butoxy aluminum hydride. One of skill in the art will recognize that they are both similar in properties and both can be used for the reduction. Moreover, the teaching by Sundberg that the reduction is slower using the tri-t-butoxide means that it reduces the lactone. Even though it may be weaker, i.e., the reaction is slower one of skill in the art would prefer to use it since the reduction reaction can be controlled and heat may be applied if needed. This is well known to one of skill in the art.

The example provided by McFarlin is the reduction of ethyl benzoate, which did not work. Ethyl benzoate, even though an ester, is not exactly the same as the lactone used instantly. Just because this one example failed doesn't mean that the reduction of an ester using lithium tri-t-butoxy aluminum hydride will not work at all. For every reaction there is always an exception. With regard to the reduction of a lactone to a lactol the teaching of Sundberg is closer to the instant case compared to that of McFarlin. One of skill in the art, reading the teaching of Sundberg will be motivated to use lithium tri-t-butoxy aluminum hydride for the said reduction because of its solubility in many solvents and also the rate is slower and more controllable.

Hence, there is reasonable expectation of success and the instant claims are rendered obvious by the prior art.

Conclusion

Claims 20, 23-28, 31-44, 50, 64-68 and 89-107 are rejected

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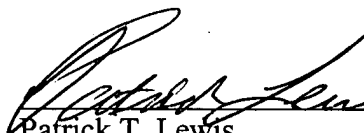
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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ganapathy Krishnan whose telephone number is 571-272-0654. The examiner can normally be reached on 8.30am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia A. Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

GK


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